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Association between rheumatoid arthritis disease activity, progression of functional limitation and long term risk of orthopaedic surgery: Combined analysis of two prospective cohorts support EULAR Treat to Target (T2T) DAS thresholds

Elena Nikiphorou[1,2], Sam Norton[3,4], Adam Young[2], Lewis Carpenter[5], Josh Dixey[6], David Andrew Walsh[7], Patrick Kiely[6] on behalf of ERAS & ERAN

[1]Department of Rheumatology, Whittington Hospital NHS Trust, London, UK

[2]Early Rheumatoid Arthritis Study, Department of Rheumatology, St Albans City Hospital, St Albans, UK

[3]Psychology Department, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[4]Division of Health & Social Care Research, Faculty of Life and Medical Science, King's College London, London, UK

[5]Centre for Lifespan & Chronic Illness Research, University of Hertfordshire, Hatfield, UK

[6]Department of Rheumatology, New Cross Hospital, Wolverhampton, UK

[7]Arthritis UK Pain Centre, University of Nottingham, Nottingham, UK

[8]Department of Rheumatology, St Georges University Hospitals NHS Foundation Trust, London, UK

Corresponding author:

Dr Elena Nikiphorou

Department of Rheumatology,

The Whittington Hospital NHS Trust,

Magdala Avenue,

London, N19 5NF

Email: elenanikiphorou@doctors.org.uk

Tel: +447990856425; Fax: +442072883498

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ABSTRACT

Objectives: To examine the association between disease activity in early RA, functional limitation and long-term orthopaedic episodes.

Methods: Health Assessment Questionnaire (HAQ) disability scores were collected from two longitudinal early RA inception cohorts in routine care; ERAS and ERAN from 1986 to 2012. The incidence of major and intermediate orthopaedic surgical episodes over 25 years was collected from national datasets. Disease activity was categorised by mean DAS28 score annually between years 1 and 5; remission [RDAS<=2.6], low [LDAS>2.6-3.2], low-moderate [LMDAS=>3.2-4.19], high-moderate [HMDAS 4.2-5.1], high [HDAS>5.1].

Results: Data from 2045 patients were analysed. Patients in RDAS showed no HAQ progression over 5 years, whereas there was a significant relationship between rising DAS28 category and HAQ at 1 year, and the rate of HAQ progression between years 1 and 5. During 27986 person-years follow-up, 392 intermediate and 591 major surgeries were observed. Compared to the RDAS category, there was a significantly increased cumulative incidence of intermediate surgery in HDAS (OR 2.59 CI 1.49-4.52) and HMDAS (OR 1.8 CI 1.05-3.11) categories, and for major surgery in HDAS (OR 2.48 CI 1.5-4.11), HMDAS (OR 2.16 CI 1.32-3.52) and LMDAS (OR 2.07 CI 1.28-3.33) categories. There was no significant difference in HAQ progression or orthopaedic episodes between RDAS and LDAS categories.

Conclusion: There is an association between disease activity and both poor function and long-term orthopaedic episodes. This illustrates the far from benign consequences of persistent moderate disease activity, and supports EULAR Treat-2-Target recommendations to secure low disease activity or remission in all patients.

(249 words)

INTRODUCTION

Treating rheumatoid arthritis (RA) to target (T2T) has become an internationally agreed standard of good practice [1] embodying the principle that rapid attainment of remission, or low disease activity, can halt joint damage and maintain good quality of life. EULAR guidelines for the management of RA are predicated on the T2T principle, and recommend use of both conventional synthetic disease modifying anti rheumatic drugs (csDMARD) and biologics (bDMARD) to achieve this. Some countries and health care systems restrict use of bDMARDs to patients with persistent disease activity score (DAS28) of 5.1 or more, [2,3] well above the suggested T2T target of 3.2.[1]

We have previously reported a low likelihood of achieving LDAS in RA patients with a DAS28 score in the moderate range, 3.2–5.1 (mDAS), using csDMARD therapies in a real world setting. In patients with mDAS at year1, only 27% achieved LDAS at year2. In those with a year1 DAS28 of 4.2-5.1, even less achieved LDAS at year2 and year3, 16% and 19% respectively.[4] The conclusion is that RA patients with mDAS at year1 are unlikely to achieve the least demanding T2T standard of LDAS with continued csDMARDs alone. These findings have been supported by other studies with high remission rates observed in patients with moderate disease starting biologics.[5–7] Similarly, longitudinal relationships between mDAS and functional disability have been reported.[7,8] However there remains an important gap in the literature on long-term outcomes of mDAS, particularly surrogate markers of joint destruction such as orthopaedic surgery.

The objectives of this study were to examine associations between disease activity during years1-5 after first presentation with i) functional outcome, measured using Health Assessment Questionnaire (HAQ), over the same period, and ii) orthopaedic interventions over a period of up to 25 years after presentation .

METHODS

Patient Databases

The Early RA Study (ERAS) is a multi-centre inception cohort which recruited 1465 early RA patients (<2 years disease duration, no prior csDMARD) between 1986-1999 from nine hospitals in England, followed yearly for up to 25 years (median follow-up 10years). The Early RA Network (ERAN) has similar design and recruited 1236 early RA patients (<3 years disease duration) from 23 centres in England, Wales and Ireland between 2002-2012 with median follow-up 6years.

Recruitment was based on clinician diagnosis with 70% of patients fulfilling the minimum ARA criteria [9] for RA at baseline and 96% by last visit.

Clinical, laboratory & functional measures

Clinical, laboratory and functional features, including rheumatoid factor (RF) status, radiographs of hand/feet and treatment, were recorded in both cohorts at baseline, between 3/6 and 12 months, then yearly on standardized case report forms (CRF),[4,10] Disease activity was calculated according to the original three variable method in ERAS (DAS) [11,12] and the more recent 4 variable DAS28 [12–14] in ERAN, compatibility achieved with a transformation formula.[15] HAQ was recorded at every patient visit.[16] Information on ACPA positivity was available for a limited number in ERAN only.

DAS28 severity over time

For the purpose of this study, disease severity over time was defined using the mean of all DAS28 recordings between years 1-5. Baseline and 3-6 month assessments were excluded due to the prevalence of non-treatment with csDMARDs at those visits. Nearly all patients had commenced csDMARDS by one year (ERAS=95.8%; ERAN=99.8%). Since there is a limited number of observations with equal time intervals, the mean DAS28 over time provides data that are equivalent to the area under the curve method of quantifying dosage. As such, the mean DAS28 can be considered as the average yearly disease activity 'dose' whilst treated. For analysis the mean year1-year5 DAS28 score for each patient was allocated into one of the following five categories: remission [RDAS <= 2.6], low [LDAS >2.6 -3.2], low-moderate [LMDAS= >3.2-4.19], high-moderate [HMDAS 4.2-5.1] or high DAS

[HDAS >5.1]. The mDAS category was split in two levels based on earlier findings in ERAN of differences in outcomes between these groups.[4]

Treatment profiles

Patients were treated according to usual care in all centres, without specific protocols, T2T or other external influences. In ERAS, csDMARD use was mainly sequential monotherapy.[17] In ERAN, more frequent and earlier use of combination csDMARD therapies and in a small proportion bDMARDs (<2% by 1year,<10% by 3years), were employed.[18] Median time from symptom-onset to first rheumatology outpatient visit was 6 months in both cohorts and time to first csDMARD initiation 1 (ERAN) to 2 (ERAS) months later.

Orthopaedic data & linkage with national datasets

Orthopaedic data from CRFs and two national datasets were merged as previously described.[19] Hospital Episode Statistics (HES) records inpatient and outpatient orthopaedic interventions undertaken at National Health Service (NHS) hospitals in England. The National Joint Registry (NJR) records hip, knee and ankle arthroplasty (more recently elbow and shoulder) undertaken in the NHS and independent healthcare sectors.

Orthopaedic interventions were categorised by joint type and procedure: [19] (1) 'major' representing large-joint arthroplasty (i.e. hips, knees, shoulders and elbows) and surgery to the cervical spine;(2) 'intermediate' representing mainly wrist, hand and hind/fore-foot reconstructive procedures (e.g. arthroplasty, synovectomy, arthrodesis).

Statistical Analysis

Summary statistics were used to describe demographic and baseline data between the mean DAS28 groups. HAQ progression between years 1-5 was estimated using linear mixed-effects modelling incorporating a within-individual random intercept and a random slope for time. Individual HAQ scores at each assessment between 1-5years were included as outcome variables. Time in years was included as a continuous variable (with random slope) allowing for the interpretation as the linear

yearly change in HAQ (annualised progression) between 1-5years. Preliminary analysis confirmed that a linear change over time provided acceptable explanatory fit, compared to a quadratic trend with acceleration of the progression rate. DAS28 category was included as dummy coded variables with an interaction term with time. This allows for the estimation of HAQ at 1year and the rate of HAQ progression for each DAS28 category, accounting for the repeated measurement of HAQ within individuals.[1] To protect against confounding, the HAQ progression analysis controlled for age at RA onset, gender, baseline RF, erosions, calendar year of first visit, current treatment using dummy coded variables for csDMARD, bDMARDS, and steroid prescription in the previous year. To avoid confounding by orthopaedic surgery, HAQ scores measured at time points following surgery were omitted. Standard errors were estimated using 1000 bootstrap resamples. Tests for differences in HAQ at 1year and rate of progression between DAS28 categories were corrected for multiple testing using the Bonferroni method (critical z-value 2.87, 5% alpha). Additional analyses, to further probe the association between DAS28 and HAQ, included mean 1-5year DAS28 as a continuous variable and, separately, individual DAS28 scores as time dependent variables.

Time in months to first intermediate or major orthopaedic intervention was estimated using multivariate competing-risks regression models with censoring at April 2011 (latest date for linkage to national datasets) with death included as a competing-risk. For individuals where linkage to national datasets was not possible (e.g. died before 1998) censoring was at last visit. As with the HAQ progression analysis, DAS28 categories were included as dummy coded variables, and the analysis protected against confounding by controlling for age at RA onset, gender and baseline HAQ, RF, erosions and calendar year of first visit.[6] Again, additional analysis included mean DAS28 as a continuous variable. All analyses were carried out in Stata 14.0.

RESULTS

Disease activity categories

[1] In additional post-hoc analyses, RF or erosion status displayed negligible effect modulation.

A total of 2045 (76%) patients had DAS28 recorded at least twice between years1-5. The mean number of DAS28 observations between 1-5years was 3.5 out of 5 possible assessments, and between baseline to 5years was 5.6 out of 7 possible assessments. Of these, using the mean DAS28 score over time, 21% were in the RDAS category, 15% in the LDAS, 26% in the LMDAS, 21% in the HMDAS, and 18% in the HDAS category. The majority of patients were observed to have DAS28 scores within the mean DAS28 category to which they were assigned on the majority of occasions (Figure 1). Only 16.4% of patients had more than half of their observations outside the range of their allocated mean DAS28 category, and 6.7% had no observations within their assigned category. The mean within-person standard deviation for DAS28 between years 1-5 was 0.84. Table 1 summarizes patient demographics, disease measures at the time of recruitment to the ERAS/ERAN cohort, csDMARD use and orthopaedic surgery by DAS28 category. Nearly all patients who were prescribed csDMARDs had started treatment by the one year assessment (ERAS=95.8%; ERAN=99.8%).

Table 1. Patient demographic, disease measures, csDMARD use and orthopaedic surgery by DAS28 category.

	DAS28 Categories				
	Remission	Low	Low Moderate	High Moderate	High
Total n (%)	425 (21)	301 (15)	524 (26)	426(21)	369(18)
Females (%)	52%	57%	69%	77%	82%
Age RA onset [mean, s.d.]	53.4, 14.0	55.5, 13.9	55.8, 13.6	55.7, 14.5	56.5, 13.6
Baseline ESR mm/hr [median, IQR]	20,32	28, 34	33, 43	37,42	42, 40
Baseline Hb [mean, s.d.]	13.1, 1.45	13.1, 1.51	12.9, 1.50	12.6, 1.60	12.4, 1.54
Baseline DAS28 [mean, s.d.]	4.00, 1.42	4.47, 1.27	4.76, 1.21	5.32, 1.16	5.82, 1.05
Baseline HAQ [mean, s.d.]	0.81,0.70	0.91, 0.70	1.07, 0.71	1.29, 0.71	1.59, 0.73

Baseline BMI [median, IQR]	25,5.28	25,4.87	26, 6.24	26, 6.58	26, 6.20
csDMARDs by 1 year (n,%)	369, 86.8%	251, 83.4%	471, 89.9%	396, 93.0%	356, 96.5%
csDMARDS weeks to start (median, IQR)	2, 0 to 6	2, 0 to 13	2, 0 to 9	2, 0 to 6	2, 0 to 6
bDMARDs by 1 year (n,%)	6, 1.4%	1, 0.3%	3, 0.6%	1, 0.2%	4, 1.1%

Disease activity and HAQ progression up to year 5

Figure 2 shows the HAQ trajectories for each of the five mean DAS28 categories. There is a clear relationship between DAS28 category and HAQ at year1 ($\chi^2(4)=682.9$, $p<.001$) and HAQ progression between years1-5 ($\chi^2(4)=51.7$, $p<.001$).

At year1, HAQ was statistically significantly higher for each DAS28 category compared to the RDAS category and, due to greater progression, was further exaggerated by year5 (all Bonferroni-corrected contrasts $p<0.05$). For the remission category HAQ at year1 was 0.304 (95%CI 0.245 - 0.363) and did not increase significantly with time (annualised progression=-0.008; p=0.345;95%CI -0.025-0.009). The LDAS category had a higher HAQ at year1 (0.522;95%CI 0.455-0.589) and experienced slow but significant progression over time (0.023;p=0.020;95%CI 0.004-0.044). The LMDAS and HMDAS categories differed in terms of HAQ at year1 (0.753;95%CI 0.703-0.803 versus 1.097;95%CI 1.041-1.153, respectively) and both progressed significantly and similarly over time (0.047;p<.001;95%CI 0.033-0.062 and 0.049;p<.001;95%CI 0.032-0.066, respectively). The HDAS category had the highest HAQ at year1 (1.555;95%CI 1.494-1.616) and experienced the most rapid rate of progression (0.078;p<.001;95%CI 0.060-0.097). Compared to the RDAS category HAQ progressed at a significantly faster rate in all other DAS28 categories, though following Bonferroni correction only the rates for the LMDAS, HMDAS and HDAS categories were significant. Compared to the LDAS category only the HDAS category progressed at a significantly faster rate (Bonferroni-corrected contrast $p<0.05$).

Analysis with mean DAS between 1-5years as a continuous variable indicated that each one unit increase in mean DAS28 score was associated with a 0.193 (95%CI 0.178-0.208;p<0.001) higher HAQ score at 1 year, and an annual HAQ progression rate that is increased by 0.005 (95%CI 0.001-0.010;p=0.023). Further analysis, including individual DAS scores at each assessment as a time-dependent variable gave similar results, although the impact of DAS28 on annualised HAQ progression was enhanced. Each one unit increase in DAS28 score at the same assessment as HAQ was associated with a 0.176 (95%CI 0.178-0.208;p<.001) higher HAQ score at 1 year, and an annual HAQ progression rate that is increased by .013 (95%CI 0.008-0.170;p<0.001).Sensitivity analysis (data not shown) indicated the same pattern of association between DAS28 category and HAQ between the ERAS and ERAN cohorts. Within each DAS28 category none of the rates of HAQ progression differed significantly between ERAS and ERAN. A further sensitivity analysis excluded patients with more than 50% of their scores outside of the DAS28 category to which they were assigned. The estimates of HAQ progression did not differ between DAS28 categories though, though confidence intervals were wider due to loss of precision.

Disease activity and prediction of orthopaedic surgery

During 27986 person-years follow-up, a total of 392 intermediate and 591 major surgeries were observed. This translates to a crude incidence rate of 14.0 (95%CI 12.7-15.5) per 1000 person-years and 21.1 (95%CI 19.4-22.9) per 1000 person-years, respectively. The 10-year cumulative incidence of intermediate surgery was 8.3% (95%CI 7.1–9.7%) and major surgery 11.7% (95%CI: 10.4–13.4%). Figures 3 and 4 show intermediate and major surgery cumulative incidence, respectively, in each of the DAS28 categories up to 25years estimated from multivariate competing-risks regression models. An increasing risk for both intermediate and major surgery was seen moving from low to moderate to high DAS28 categories (Table 2).

Table 2. Hazard Ratios (95% CI) for intermediate and major orthopaedic surgery by DAS28 category

	DAS28 category

	Remission^	Low	Low Moderate	High Moderate	High
Intermediate surgery	1.00	1.13 (0.60-2.11)	1.33 (0.77-2.29)	1.80* (1.05-3.11)	2.59* (1.49-4.52)
Major surgery	1.00	1.65 (0.97-2.80)	2.07** (1.28-3.33)	2.16** (1.32-3.52)	2.48** (1.50-4.11)

*^Reference category against which other DAS28 categories are compared. *p<0.001; ** p<0.05.*

Compared to patients in the RDAS category, there was a significantly increased cumulative incidence of intermediate surgery observed in patients in the HMDAS (HR 1.8;95%CI 1.05-3.11) and HDAS (HR 2.59;95%CI 1.49-4.52) categories, and for major surgery a significantly increased cumulative incidence in patients in the HDAS (HR 2.48;95%CI 1.5-4.11), HMDAS (HR 2.16;95%CI 1.32-3.52) and LMDAS (HR 2.07;95%CI 1.28-3.33) categories (Table 2). Comparing the LDAS with the RDAS category, the HR for major and intermediate surgery was 1.65 and 1.13 respectively, but no statistical significance was reached (p>0.05).

Further analysis including DAS as a continuous, rather than categorical, variable also supported the relationship between disease activity and increased risk of both intermediate (HR 1.31;95%CI 1.15-1.48) and major surgery (HR 1.22;95%CI 1.10-1.36).

A sensitivity analysis was performed with the analysis conducted separately for each cohort (data not shown). The same increasing trend in HR was observed for increasing DAS28 category with no substantive difference in the estimates between cohorts. A further sensitivity analysis excluded patients with more than 50% of their scores outside of the DAS category to which they were assigned. The HR estimates for each DAS28 category did not differ substantively compared to the original analysis.

DISCUSSION

This study reports on functional and orthopaedic surgery outcomes in two large RA inception cohorts, both surrogate markers for failed medical management. [20-23] Our findings demonstrate an association between increasing disease activity, measured by mean DAS28 after csDMARD initiation, and functional limitation, measured by absolute HAQ scores and the rate of progression of HAQ over 5years. Patients in the RDAS category had no HAQ progression, demonstrating that functional preservation is achievable; as embodied in the T2T principles.[1] Whilst predictably patients in the HDAS category showed the highest functional limitation and progression, those in the LMDAS and HMDAS categories also demonstrated significantly greater progression than the RDAS category, illustrating that these are not benign states.

The orthopaedic data support these findings, demonstrating that the cumulative incidence of intermediate and major surgery over 25years is associated with disease activity between years1-5. In particular, patients in the LMDAS and HMDAS categories had a significantly higher prevalence of major surgery compared to those in RDAS and this was also true for intermediate surgery for those in HMDAS, illustrating the far from benign consequences of sustained mDAS and csDMARD therapy between years1-5. These findings highlight the long-term health burden in RA patients not achieving early and sustained remission.

Our results are supported by data from the ESPOIR cohort [8] where patients with early RA and persistent mDAS demonstrated adverse outcomes, compared to those in sustained remission during the first year; evidenced by increased 3-year radiographic progression, increased HAQ-DI at 3 and 5years, and a fivefold increase in missed workdays over 5years.

The observations made in our study have critical implications in countries like England and Wales where eligibility criteria to commence bDMARDs are based on DAS28 thresholds which exclude moderate disease.[2] This applies to as many as 47% of patients in ERAS/ERAN who were categorized in the mDAS range between years1-5, and would not be permitted bDMARDs by NICE. In contrast, Swedish data reports that half of all first time TNF inhibitor starters in 2011 had a DAS28

<5.2.[24] Furthermore data from the ARTIS register demonstrates the cost-effectiveness of bDMARDs mDAS and HDAS.[25] Others have demonstrated the clinical benefits of starting bDMARDs earlier and at lower disease activity levels including mDAS.[7,26] It is therefore evident that bDMARDs are effective when used as part of a T2T strategy [1]. In contrast, our data reveal the adverse consequences when restrictive health care systems deny mDAS patients such therapies.

Intriguingly when comparing the LDAS and RDAS categories, similar functional and orthopaedic outcomes were seen. The annual rate of HAQ progression in the general population aged over 50 has been reported to be 0.01.[27] Our findings for the RDAS (-0.008) and LDAS (0.023) groups between years1–5 are not significantly different from this, nor from each other. In terms of orthopaedic episodes, the differences observed between the LDAS and RDAS categories for intermediate and major surgery were also not statistically significant. This prompts the question, whether in a T2T strategy it is necessary to reduce disease activity as low as remission, or alternatively whether LDAS is sufficient. Our data would seem to support the EULAR recommendation that LDAS is an acceptable target in patients with established disease.[1]

The real-life setting, large patient numbers and long follow-up are strengths that have enabled an analysis of the consequences of a range of disease activity states in the first 5 years on function and orthopaedic episodes up to 25 years later. The linkage with national datasets and high follow-up rates add to the validity and accuracy of data examined. HAQ is recognised as a predictor of key outcomes of disease such as mortality,[28-30] work disability [31-33] and healthcare resource utilization [34] and is therefore a powerful outcome measure. This analysis controlled for key parameters of disease which could have influenced the results including year of first visit (as an indirect measure of treatment strategies employed at different times), treatment using dummy coded variables for csDMARDs, and bDMARDs, and steroid prescription in the previous year. However, the approach used does not fully account for confounding by indication, therefore it is not possible to make specific causal inferences about the impact of different treatment regimens on outcome.[35]

In our analysis, allocation of patients into one of five DAS28 categories as an indicator of disease severity over time was based on the mean DAS28 score between years 1-5. This represents average disease activity per patient but does not imply that patients will have spent all of the study period persistently in the DAS28 category to which they were allocated, nor indeed that there is no fluctuation in DAS28 scores over time. Findings for the means DAS28 groupings should be considered in terms of the annual 'dose' of DAS28, whilst on treatment. Nevertheless, as only 16.4% of patients (Figure 1) had more than half of their observations outside the range of their category, for many the allocated DAS category indicates a relatively persistent state. This reflects the inability of standard care at that time (largely in the absence of bDMARDs), to achieve contemporary T2T outcomes. A limitation is that, though DAS28 and HAQ data were available beyond 5-years for both cohorts, the number of ERAN patients who provided data beyond 5 years was limited due to recent recruitment. Restricting the analysis to the first 5-years, during which the disease progresses from early to established, increases likely generalisability to modern patients treated with csDMARDs.'This study illustrates an association between disease activity and both progression of functional limitation and orthopaedic episodes in RA, with incremental differences apparent in all DAS28 categories, compared to RDAS. This supports the selection of a DAS28 score no higher than 3.2 as a T2T outcome, and in our opinion provides a strong argument for maximising treatment interventions when this has not been achieved. Our data may be used to inform guidelines and recommendations for the use of more intensive therapies including bDMARDs in RA patients with persistent mDAS. We hope this will translate into a more harmonized approach to the management of RA across the globe with fresh imperatives to adopt T2T strategies to achieve remission or LDAS for the majority of patients.

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COMPETING INTERESTS

EN, SN, AY, LC, JD, DAW and PK have no conflicts of interest to declare.

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ETHICAL APPROVAL

The ERAS study received ethical approval from the West Hertfordshire Local Research Ethics Committee and subsequently from the Caldicott Guardian. The ERAN study received ethical approval by the Trent Research Ethics Committee.

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Figure 1. DAS 28 scores from year 1 to 5 by disease activity category.

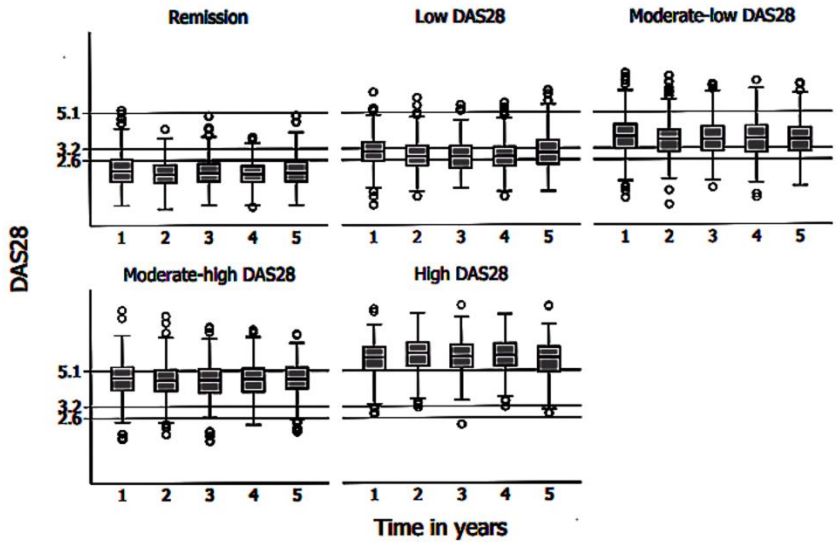


Figure 2. HAQ progression by DAS28 category. Shaded areas indicate 95% confidence intervals.

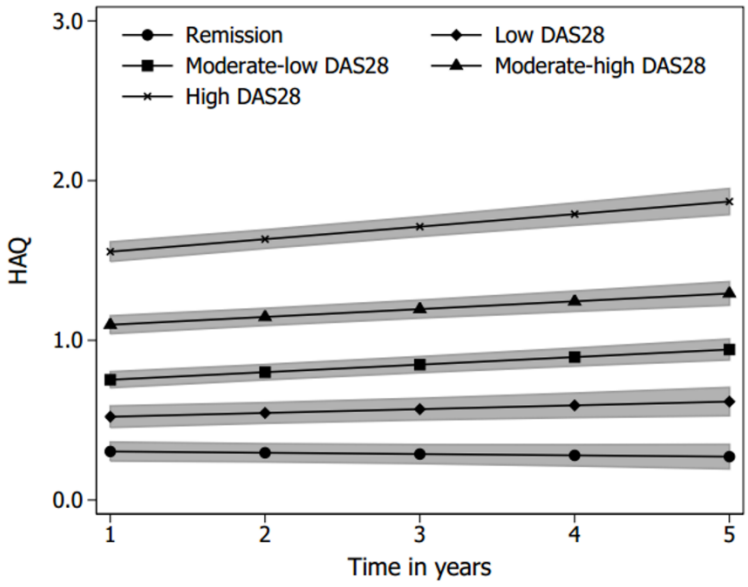


Figure 3. Cumulative incidence for intermediate orthopaedic surgery by DAS28 category over time.

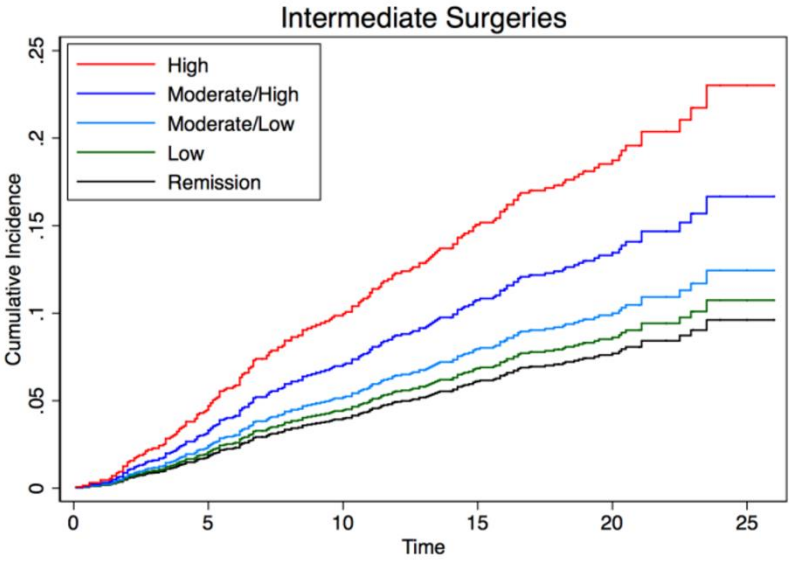
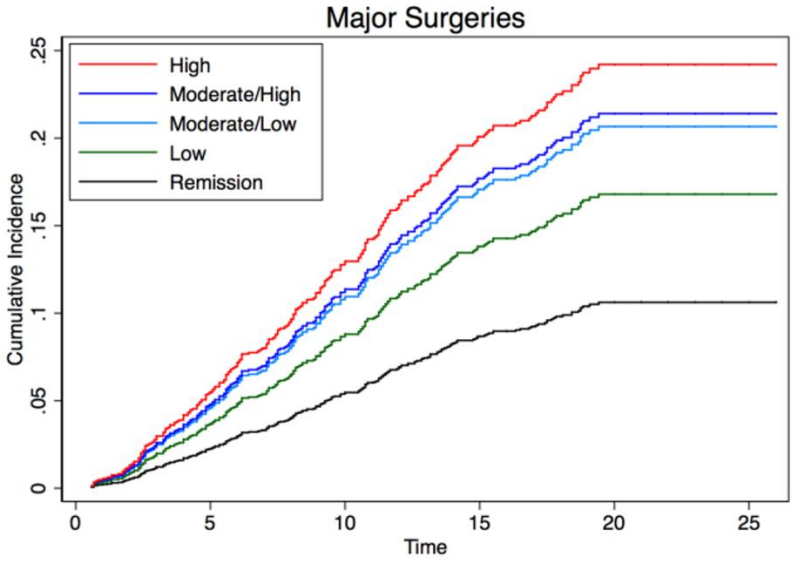


Figure 4. Cumulative incidence for major orthopaedic surgery by DAS28 category over time.


Major Surgeries
High
Moderate/High
Moderate/Low
Low
Remission
Cumulative Incidence
0
.05
.1
.15
.2
.25
0
5
10
15
20
25
Time